coupling on ($[Ca^{2+}]_i$) dynamics. We have found that by re-aggregating β-cells, they return to a native-like oscillatory behavior, which is lost in 2D cultures. In addition, the overall coordination of 2D clusters was found to decrease with cluster size, showing distinct sub-regions of coordination, while the 3D cultures were better coordinated at comparable sizes and cell numbers.
Using a percolation-based theory for modeling cell coordination, we show how higher dimensions of coupling lead to better overall synchrony with larger regions of coordination. This model also predicts the distances over which coupled cells can communicate. This has broader implications in that a loss of cell coupling and a reduction in coordination and responsiveness are often seen in islets from models of type2 diabetes. Also, the application of our mathematical model to predict cellular phenomena yields new insight in understanding the coordinated behavior of electrophysiological signaling in general.

2512-Pos Board B531
Cardiac Myocytes Expressing Disease-Causing Mutant Plakoglobin Exhibit Alterations in Mechanotransduction
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Introduction: Mechanotransduction is the process by which cells couple their external and internal environments by transducing mechanical stimuli into a biochemical response. While this process is responsible for regulating cell fate through gene expression (i.e. - *c-myc*, *c-fos*, etc.), it remains incompletely characterized in cardiac myocytes. Our previous work demonstrated that primary neonatal rat ventricular myocytes (NRVM) respond to mechanical shear stress via junctional remodeling of plakoglobin (JUP) and N-cadherin (NC). Here, we study myocyte mechanotransduction by investigating ERK phosphorylation, c-myc & c-fos gene regulation; we also investigate the effects of inhibiting primary cilia in NRVM, one potential mechanism for transduction of mechanical stimuli.
Methods: NRVM were transfected with adenoviruses to express either of two different mutations in JUP (2057del2 & S39_K40insS) which cause arrhythmogenic right ventricular cardiomyopathy (ARVC). Primary cilia were inhibited by transfecting NRVM with siRNA against intraflagellar transport protein 88 (IFT88). NRVM were sheared under oscillatory flow in a parallel-plate shear chamber at physiologically-relevant shear stresses (forces in the plane of the cell layer that mimic those in contracting myocardium; 0.06 Pascal). Samples were subsequently stained and imaged on an Olympus IX-81 confocal microscope using quantitative confocal microscopy. Immunoblotting was performed on NRVM lysates separated by PAGE.
Conclusions: We demonstrate that ERK phosphorylation, and c-myc & c-fos regulation are unaffected by mutant JUP expression. Our previous results indicate that cardiac myocytes are responsive to shear stimuli, and undergo junctional remodeling of both NC and JUP under oscillatory shear, a phenomenon absent in cells expressing ARVC-causing mutant JUP. Interestingly, knockdown of IFT88 does not have a dramatic effect on junctional remodeling; these results suggest that the role of primary cilia in cardiomyocyte shear sensing is varied and does not affect all shear-dependent pathways.

2513-Pos Board B532
Mechanosensitivity and Motility of Cellular Aggregates
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We describe the biomechanics of multicellular aggregates, a model system for tissues and tumors. We first characterize the tissue mechanical properties (surface tension, elasticity, viscosity) by a new pipette aspiration technique. The aggregate exhibits a viscoelastic response but, unlike an inert fluid, we observe aggregate reinforcement with pressure, which for a narrow range of pressures results in pulsed contractions or ''shivering''. We interpret this reinforcement as a mechanosensitive active response of the acto-myosin cortex. Such an active behavior has previously been found to cause tissue pulsation during dorsal closure of Drosophila embryo.
We then describe aggregate spreading on decorated glass substrates. We find a universal spreading law at short time, analogous to that of a viscoelastic drop. At long time, we observe a precursor film spreading around the aggregate. Depending on aggregate cohesion, this precursor film can be a dense cellular monolayer (''liquid state'') or consist of individual cells escaping from the aggregate body (''gas state''). The transition from ''liquid'' to ''gas state'' appears also to be present in the progression of a tumor from noninvasive to metastatic, known as the epithelial-mesenchymal transition.
Finally, we describe the effect of the substrate rigidity on the spreading of aggregates. We observe that aggregates spreading on rigid gels , do not spread on soft gels: we can induce a wetting transition from complete to partial wetting by decreasing the elastic modulus of the substrate. Moreover, near this transition, we observe a spontaneous motion of the aggregates, where all cells have a cooperative motion forming a giant keratocytes.

2514-Pos Board B533
Mechanical Pressure Arrests the Growth of Tumor Spheroids
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Often tumors have to push their surroundings in order to grow. Thus, during their development, tumors must be able to both exert and sustain mechanical stresses. We study quantitatively the effect of an applied mechanical stress on the long-term growth of a spherical cell aggregate. Our results indicate the possibility to modulate tumor growth depending on the applied pressure. Moreover, we observe that a stress between 500 and 5000 Pa drastically reduces growth by inhibition of cell proliferation mainly in the core of the spheroid, while it sligthly affect the division at the perifery.

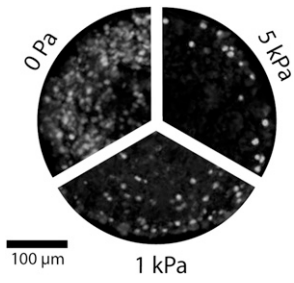

FIGURE: Three cryosections of a spheroid grown for 2 days without stress, with a stress of 1 kPa or with a stress of 5 kPa. Dividing cells are stained incyan (Antibody against Ki67).

2515-Pos Board B534
Gap-Junction Suppression of Electrical Activity in Normal and Diabetic Pancreatic Islets
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The pancreatic islets of Langerhans are multicellular microorgans which play a central role in maintaining blood glucose homeostasis, through secretion of hormone insulin. Interactions between cells within the islet are critical to enhance and coordinate the β-cell insulin secretion response to glucose. Gap junction channels coordinate membrane potential between β-cells in the islet. This serves to coordinate oscillations in free-calcium activity ($[Ca^{2+}]_i$) and insulin secretion, but also to suppress spontaneous $[Ca^{2+}]_i$ elevations under basal glucose.
Here we quantify the gap junction suppression of β-cell excitability and describe this with a percolation model of cell-cell coupling. We utilize islets from wild-type mice and 2 transgenic mouse models in which mutations to the K_{ATP} channel either increase or decrease excitability in a population of β-cells in the islet. In each set of islets, we quantify the variation of $[Ca^{2+}]_i$ and insulin secretion with gap junction coupling, at low glucose and high glucose. In all cases reduced gap junction coupling resulted in elevated $[Ca^{2+}]_i$; with the variation of $[Ca^{2+}]_i$ with gap junction conductance showing a similar non-linear relationship which can be described using the percolation model. This variation could also describes insulin release and glucose homeostasis: large elevations in $[Ca^{2+}]_i$ predict significant reductions in blood glucose levels. Importantly, in mice expressing K_{ATP} channel mutations that reduce insulin secretion and cause severe hyperglycemia and diabetes, a reduction in gap junction coupling elevates insulin release and prevents diabetes.
Thus the relationship governing gap junction coupling and the suppression of spontaneous elevations in $[Ca^{2+}]_i$ is dependent on the distribution of excitability across β-cells of the islet and the level of coupling between β-cells, and this governs the overall islet response. Utilizing this may be a promising therapeutic treatment for specific monogenic forms of diabetes.

2516-Pos Board B535
Is the Gain of Hemichannel Activity a Common Feature Shared by Cx26 Syndromic Deafness Mutants?
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Gap junctions and hemichannels (HCs) are major pathways for intercellular signaling. Both are made of homologous proteins named connexins. Mutations in the gene encoding Cx26 account for a large proportion of genetic deafness. These can lead to non-syndromic and syndromic deafness. The syndromic phenotype also includes awful skin disease. Gain of hemichannel activity has been proposed as the pathogenic mechanism behind this syndrome. Here, to test this hypothesis we used HeLa cells transiently expressing the Cx26 non-syndromic (G12V) and the syndromic (G12R, N14Y and S17F), all located